

PRESCRIBING INFORMATION

ZYBAN[®]
(bupropion hydrochloride)
Sustained-Release Tablets

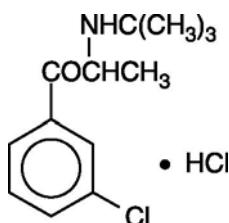
Suicidality in Children and Adolescents

Although ZYBAN is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications WELLBUTRIN[®], WELLBUTRIN SR[®], and WELLBUTRIN XL[®]. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of ZYBAN or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ZYBAN is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

ZYBAN (bupropion hydrochloride) Sustained-Release Tablets are a non-nicotine aid to smoking cessation. ZYBAN is chemically unrelated to nicotine or other agents currently used in the treatment of nicotine addiction. Initially developed and marketed as an antidepressant (WELLBUTRIN [bupropion hydrochloride] Tablets and WELLBUTRIN SR [bupropion hydrochloride] Sustained-Release Tablets), ZYBAN is also chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is C₁₃H₁₈ClNO•HCl. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



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41 ZYBAN Tablets are supplied for oral administration as 150-mg (purple), film-coated,
42 sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride
43 and the inactive ingredients carnauba wax, cysteine hydrochloride, hypromellose, magnesium
44 stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide and
45 is printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake
46 and FD&C Red No. 40 Lake.

47 **CLINICAL PHARMACOLOGY**

48 **Pharmacodynamics:** Bupropion is a relatively weak inhibitor of the neuronal uptake of
49 norepinephrine and dopamine, and does not inhibit monoamine oxidase or the re-uptake of
50 serotonin. The mechanism by which ZYBAN enhances the ability of patients to abstain from
51 smoking is unknown. However, it is presumed that this action is mediated by noradrenergic
52 and/or dopaminergic mechanisms.

53 **Pharmacokinetics:** Bupropion is a racemic mixture. The pharmacologic activity and
54 pharmacokinetics of the individual enantiomers have not been studied. Bupropion follows
55 biphasic pharmacokinetics best described by a 2-compartment model. The terminal phase has a
56 mean half-life (\pm % CV) of about 21 hours (\pm 20%), while the distribution phase has a mean
57 half-life of 3 to 4 hours.

58 **Absorption:** Bupropion has not been administered intravenously to humans; therefore,
59 the absolute bioavailability of ZYBAN Sustained-Release Tablets in humans has not been
60 determined. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

61 Following oral administration of ZYBAN to healthy volunteers, peak plasma
62 concentrations of bupropion are achieved within 3 hours. The mean peak concentration (C_{max})
63 values were 91 and 143 ng/mL from 2 single-dose (150-mg) studies. At steady state, the mean
64 C_{max} following a 150-mg dose every 12 hours is 136 ng/mL.

65 In a single-dose study, food increased the C_{max} of bupropion by 11% and the extent of
66 absorption as defined by area under the plasma concentration-time curve (AUC) by 17%. The
67 mean time to peak concentration (T_{max}) was prolonged by 1 hour. This effect was of no clinical
68 significance.

69 **Distribution:** In vitro tests show that bupropion is 84% bound to human plasma proteins
70 at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion
71 metabolite is similar to that for bupropion, whereas the extent of protein binding of the
72 threohydrobupropion metabolite is about half that seen with bupropion. The volume of
73 distribution (V_{ss}/F) estimated from a single 150-mg dose given to 17 subjects is 1,950 L
74 (20% CV).

75 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have
76 been shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl
77 group of bupropion, and the amino-alcohol isomers threohydrobupropion and
78 erythrohydrobupropion, which are formed via reduction of the carbonyl group. In vitro findings
79 suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the
80 formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the
81 formation of threohydrobupropion. Oxidation of the bupropion side chain results in the
82 formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major
83 urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not
84 been fully characterized. However, it has been demonstrated in an antidepressant screening test

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85 in mice that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion
86 and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical
87 importance because the plasma concentrations of the metabolites are as high or higher than those
88 of bupropion.

89 Because bupropion is extensively metabolized, there is the potential for drug-drug
90 interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6
91 (CYP2B6) isoenzyme. Although bupropion is not metabolized by cytochrome P450IID6
92 (CYP2D6), there is the potential for drug-drug interactions when bupropion is co-administered
93 with drugs metabolized by this isoenzyme (see PRECAUTIONS: Drug Interactions).

94 Following a single dose in humans, peak plasma concentrations of hydroxybupropion
95 occur approximately 6 hours after administration of ZYBAN Tablets. Peak plasma
96 concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug
97 at steady state. The elimination half-life of hydroxybupropion is approximately 20 (± 5) hours,
98 and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations
99 for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the
100 hydroxybupropion metabolite; however, their elimination half-lives are longer, 33 (± 10) and
101 37 (± 13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion,
102 respectively.

103 Bupropion and its metabolites exhibit linear kinetics following chronic administration of
104 300 to 450 mg/day.

105 **Elimination:** The mean (\pm % CV) apparent clearance (Cl/F) estimated from 2
106 single-dose (150-mg) studies are 135 (± 20 %) and 209 L/hr (± 21 %). Following chronic dosing of
107 150 mg of ZYBAN every 12 hours for 14 days (n = 34), the mean Cl/F at steady state was
108 160 L/hr (± 23 %). The mean elimination half-life of bupropion estimated from a series of studies
109 is approximately 21 hours. Estimates of the half-lives of the metabolites determined from a
110 multiple-dose study were 20 hours (± 25 %) for hydroxybupropion, 37 hours (± 35 %) for
111 threohydrobupropion, and 33 hours (± 30 %) for erythrohydrobupropion. Steady-state plasma
112 concentrations of bupropion and metabolites are reached within 5 and 8 days, respectively.

113 Following oral administration of 200 mg of ^{14}C -bupropion in humans, 87% and 10% of
114 the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral
115 dose of bupropion excreted unchanged was only 0.5%.

116 The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in
117 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were
118 nonsmokers. Following oral administration of a single 150-mg dose of ZYBAN, there was no
119 statistically significant difference in C_{max} , half-life, T_{max} , AUC, or clearance of bupropion or its
120 major metabolites between smokers and nonsmokers.

121 In a study comparing the treatment combination of ZYBAN and nicotine transdermal
122 system (NTS) versus ZYBAN alone, no statistically significant differences were observed
123 between the 2 treatment groups of combination ZYBAN and NTS (n = 197) and ZYBAN alone
124 (n = 193) in the plasma concentrations of bupropion or its active metabolites at weeks 3 and 6.

125 **Population Subgroups:** Factors or conditions altering metabolic capacity (e.g., liver disease,
126 congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be
127 expected to influence the degree and extent of accumulation of the active metabolites of
128 bupropion. The elimination of the major metabolites of bupropion may be affected by reduced
129 renal or hepatic function because they are moderately polar compounds and are likely to undergo
130 further metabolism or conjugation in the liver prior to urinary excretion.

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131 **Hepatic:** The effect of hepatic impairment on the pharmacokinetics of bupropion was
132 characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in
133 patients with mild to severe cirrhosis. The first study showed that the half-life of
134 hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8
135 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically
136 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be
137 greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for
138 bupropion and the other metabolites in the 2 patient groups were minimal.

139 The second study showed that there were no statistically significant differences in the
140 pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate
141 hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in
142 some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active
143 metabolites (t_{1/2}) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with
144 severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean
145 difference: by approximately 70% and 3-fold, respectively) and more variable when compared to
146 values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients
147 with severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite
148 hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-
149 alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was
150 approximately 31% lower. The mean AUC increased by 28% for hydroxybupropion and 50% for
151 threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for
152 hydroxybupropion and 21 hours later for threo/erythrohydrobupropion. The mean half-lives for
153 hydroxybupropion and threo/erythrohydrobupropion were increased 2- and 4-fold, respectively,
154 in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS,
155 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

156 **Renal:** There is limited information on the pharmacokinetics of bupropion in patients
157 with renal impairment. An inter-study comparison between normal subjects and patients with
158 end-stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable
159 in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3-
160 and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. The
161 elimination of the major metabolites of bupropion may be reduced by impaired renal function
162 (see PRECAUTIONS: Renal Impairment).

163 **Left Ventricular Dysfunction:** During a chronic dosing study with bupropion in
164 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on
165 x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared to
166 healthy normal volunteers, was revealed.

167 **Age:** The effects of age on the pharmacokinetics of bupropion and its metabolites have
168 not been fully characterized, but an exploration of steady-state bupropion concentrations from
169 several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on
170 a 3 times a day schedule, revealed no relationship between age (18 to 83 years) and plasma
171 concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the
172 disposition of bupropion and its metabolites in elderly subjects was similar to that of younger
173 subjects. These data suggest there is no prominent effect of age on bupropion concentration;
174 however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly
175 are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS:
176 Geriatric Use).

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177 **Gender:** A single-dose study involving 12 healthy male and 12 healthy female
178 volunteers revealed no sex-related differences in the pharmacokinetic parameters of bupropion.

179 **CLINICAL TRIALS**

180 The efficacy of ZYBAN as an aid to smoking cessation was demonstrated in
181 3 placebo-controlled, double-blind trials in nondepressed chronic cigarette smokers (n = 1,940,
182 ≥15 cigarettes per day). In these studies, ZYBAN was used in conjunction with individual
183 smoking cessation counseling.

184 The first study was a dose-response trial conducted at 3 clinical centers. Patients in this
185 study were treated for 7 weeks with 1 of 3 doses of ZYBAN (100, 150, or 300 mg/day) or
186 placebo; quitting was defined as total abstinence during the last 4 weeks of treatment (weeks 4
187 through 7). Abstinence was determined by patient daily diaries and verified by carbon monoxide
188 levels in expired air.

189 Results of this dose-response trial with ZYBAN demonstrated a dose-dependent increase
190 in the percentage of patients able to achieve 4-week abstinence (weeks 4 through 7). Treatment
191 with ZYBAN at both 150 and 300 mg/day was significantly more effective than placebo in this
192 study.

193 Table 1 presents quit rates over time in the multicenter trial by treatment group. The quit
194 rates are the proportions of all persons initially enrolled (i.e., intent to treat analysis) who
195 abstained from week 4 of the study through the specified week. Treatment with ZYBAN (150 or
196 300 mg/day) was more effective than placebo in helping patients achieve 4-week abstinence. In
197 addition, treatment with ZYBAN (7 weeks at 300 mg/day) was more effective than placebo in
198 helping patients maintain continuous abstinence through week 26 (6 months) of the study.
199

200 **Table 1. Dose-Response Trial: Quit Rates by Treatment Group**

	Treatment Groups			
	Placebo (n = 151) % (95% CI)	ZYBAN 100 mg/day (n = 153) % (95% CI)	ZYBAN 150 mg/day (n = 153) % (95% CI)	ZYBAN 300 mg/day (n = 156) % (95% CI)
Abstinence From Week 4 Through Specified Week				
Week 7 (4-week quit)	17% (11-23)	22% (15-28)	27%* (20-35)	36%* (28-43)
Week 12	14% (8-19)	20% (13-26)	20% (14-27)	25%* (18-32)
Week 26	11% (6-16)	16% (11-22)	18% (12-24)	19%* (13-25)

201 *Significantly different from placebo ($p \leq 0.05$).
202

203 The second study was a comparative trial conducted at 4 clinical centers. Four treatments
204 were evaluated: ZYBAN 300 mg/day, nicotine transdermal system (NTS) 21 mg/day,
205 combination of ZYBAN 300 mg/day plus NTS 21 mg/day, and placebo. Patients were treated for
206 9 weeks. Treatment with ZYBAN was initiated at 150 mg/day while the patient was still
207 smoking and was increased after 3 days to 300 mg/day given as 150 mg twice daily. NTS
208 21 mg/day was added to treatment with ZYBAN after approximately 1 week when the patient

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209 reached the target quit date. During weeks 8 and 9 of the study, NTS was tapered to 14 and
210 7 mg/day, respectively. Quitting, defined as total abstinence during weeks 4 through 7, was
211 determined by patient daily diaries and verified by expired air carbon monoxide levels. In this
212 study, patients treated with any of the 3 treatments achieved greater 4-week abstinence rates than
213 patients treated with placebo.

214 Table 2 presents quit rates over time by treatment group for the comparative trial.
215

216 **Table 2. Comparative Trial: Quit Rates by Treatment Group**

Abstinence From Week 4 Through Specified Week	Treatment Groups			
	Placebo (n = 160) % (95% CI)	Nicotine Transdermal System (NTS) 21 mg/day (n = 244) % (95% CI)	ZYBAN 300 mg/day (n = 244) % (95% CI)	ZYBAN 300 mg/day and NTS 21 mg/day (n = 245) % (95% CI)
Week 7 (4-week quit)	23% (17-30)	36% (30-42)	49% (43-56)	58% (51-64)
Week 10	20% (14-26)	32% (26-37)	46% (39-52)	51% (45-58)

217
218 When patients in this study were followed out to one year, the superiority of ZYBAN and
219 the combination of ZYBAN and NTS over placebo in helping patients to achieve abstinence
220 from smoking was maintained. The continuous abstinence rate was 30% (95% CI 24-35) in the
221 ZYBAN treated patients, and 33% (95% CI 27-39) for patients treated with the combination at
222 26 weeks compared with 13% (95% CI 7-18) in the placebo group. At 52 weeks, the continuous
223 abstinence rate was 23% (95% CI 18-28) in the ZYBAN treated patients, and 28% (95% CI
224 23-34) for patients treated with the combination, compared with 8% (95% CI 3-12) in the
225 placebo group. Although the treatment combination of ZYBAN and NTS displayed the highest
226 rates of continuous abstinence throughout the study, the quit rates for the combination were not
227 significantly higher ($p>0.05$) than for ZYBAN alone.

228 The comparisons between ZYBAN, NTS, and combination treatment in this study have
229 not been replicated, and, therefore should not be interpreted as demonstrating the superiority of
230 any of the active treatment arms over any other.

231 The third study was a long-term maintenance trial conducted at 5 clinical centers. Patients
232 in this study received open-label ZYBAN 300 mg/day for 7 weeks. Patients who quit smoking
233 while receiving ZYBAN (n = 432) were then randomized to ZYBAN 300 mg/day or placebo for
234 a total study duration of 1 year. Abstinence from smoking was determined by patient self-report
235 and verified by expired air carbon monoxide levels. This trial demonstrated that at 6 months,
236 continuous abstinence rates were significantly higher for patients continuing to receive ZYBAN
237 than for those switched to placebo ($p<0.05$; 55% versus 44%).

238 Quit rates in clinical trials are influenced by the population selected. Quit rates in an
239 unselected population may be lower than the above rates. Quit rates for ZYBAN were similar in
240 patients with and without prior quit attempts using nicotine replacement therapy.

241 Treatment with ZYBAN reduced withdrawal symptoms compared to placebo. Reductions on
242 the following withdrawal symptoms were most pronounced: irritability, frustration, or anger;

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243 anxiety; difficulty concentrating; restlessness; and depressed mood or negative affect. Depending
244 on the study and the measure used, treatment with ZYBAN showed evidence of reduction in
245 craving for cigarettes or urge to smoke compared to placebo.

246 **Use In Patients With Chronic Obstructive Pulmonary Disease (COPD):** ZYBAN was
247 evaluated in a randomized, double-blind, comparative study of 404 patients with mild-to-
248 moderate COPD, defined as $FEV_1 \geq 35\%$, $FEV_1/FVC \leq 70\%$ and a diagnosis of chronic bronchitis,
249 emphysema and/or small airways disease. Patients aged 36 to 76 years were randomized to
250 ZYBAN 300 mg/day (n = 204) or placebo (n = 200) and treated for 12 weeks. Treatment with
251 ZYBAN was initiated at 150 mg/day for 3 days while the patient was still smoking and increased
252 to 150 mg twice daily for the remaining treatment period. Abstinence from smoking was
253 determined by patient daily diaries and verified by carbon monoxide levels in expired air.
254 Quitters are defined as subjects who were abstinent during the last 4 weeks of treatment. Table
255 3 shows quit rates in the COPD Trial.
256

257 **Table 3. COPD Trial: Quit Rates by Treatment Group**

	Treatment Groups	
	Placebo (n = 200) % (95% CI)	ZYBAN 300 mg/day (n = 204) % (95% CI)
4-Week Abstinence Period		
Weeks 9 through 12	12% (8-16)	22%* (17-27)

258 *Significantly different from placebo ($p < 0.05$).

259 INDICATIONS AND USAGE

260 ZYBAN is indicated as an aid to smoking cessation treatment.

261 CONTRAINDICATIONS

262 ZYBAN is contraindicated in patients with a seizure disorder.

263 ZYBAN is contraindicated in patients treated with WELLBUTRIN (bupropion
264 hydrochloride), the immediate-release formulation; WELLBUTRIN SR (bupropion
265 hydrochloride), the sustained-release formulation; WELLBUTRIN XL (bupropion
266 hydrochloride), the extended-release formulation; or any other medications that contain
267 bupropion because the incidence of seizure is dose dependent.

268 ZYBAN is contraindicated in patients with a current or prior diagnosis of bulimia or
269 anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia
270 with the immediate-release formulation of bupropion.

271 ZYBAN is contraindicated in patients undergoing abrupt discontinuation of alcohol or
272 sedatives (including benzodiazepines).

273 The concurrent administration of ZYBAN and a monoamine oxidase (MAO) inhibitor is
274 contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and
275 initiation of treatment with ZYBAN.

276 ZYBAN is contraindicated in patients who have shown an allergic response to bupropion
277 or the other ingredients that make up ZYBAN.

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278 **WARNINGS**

279 **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder (MDD),
280 both adult and pediatric, may experience worsening of their depression and/or the emergence of
281 suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they
282 are taking antidepressant medications, and this risk may persist until significant remission
283 occurs. There has been a long-standing concern that antidepressants may have a role in inducing
284 worsening of depression and the emergence of suicidality in certain patients. Antidepressants
285 increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children
286 and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

287 Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs
288 and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total
289 of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events
290 representing suicidal behavior or thinking (suicidality) during the first few months of treatment
291 in those receiving antidepressants. The average risk of such events in patients receiving
292 antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk
293 among drugs, but a tendency toward an increase for almost all drugs studied. The risk of
294 suicidality was most consistently observed in the MDD trials, but there were signals of risk
295 arising from some trials in other psychiatric indications (obsessive compulsive disorder and
296 social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown
297 whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several
298 months. It is also unknown whether the suicidality risk extends to adults.

299 **All pediatric patients being treated with antidepressants for any indication should**
300 **be observed closely for clinical worsening, suicidality, and unusual changes in behavior,**
301 **especially during the initial few months of a course of drug therapy, or at times of dose**
302 **changes, either increases or decreases. Such observation would generally include at least**
303 **weekly face-to-face contact with patients or their family members or caregivers during the**
304 **first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at**
305 **12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may**
306 **be appropriate between face-to-face visits.**

307 **Adults with MDD or co-morbid depression in the setting of other psychiatric illness**
308 **being treated with antidepressants should be observed similarly for clinical worsening and**
309 **suicidality, especially during the initial few months of a course of drug therapy, or at times**
310 **of dose changes, either increases or decreases.**

311 **In addition, patients with a history of suicidal behavior or thoughts, those patients**
312 **exhibiting a significant degree of suicidal ideation prior to commencement of treatment,**
313 **and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and**
314 **should receive careful monitoring during treatment.**

315 The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility,
316 aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have
317 been reported in adult and pediatric patients being treated with antidepressants for major
318 depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.
319 Although a causal link between the emergence of such symptoms and either the worsening of
320 depression and/or the emergence of suicidal impulses has not been established, there is concern
321 that such symptoms may represent precursors to emerging suicidality.

322 Consideration should be given to changing the therapeutic regimen, including possibly
323 discontinuing the medication, in patients whose depression is persistently worse, or who are

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324 experiencing emergent suicidality or symptoms that might be precursors to worsening depression
325 or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the
326 patient's presenting symptoms.

327 **Families and caregivers of pediatric patients being treated with antidepressants for**
328 **major depressive disorder or other indications, both psychiatric and nonpsychiatric,**
329 **should be alerted about the need to monitor patients for the emergence of agitation,**
330 **irritability, unusual changes in behavior, and the other symptoms described above, as well**
331 **as the emergence of suicidality, and to report such symptoms immediately to health care**
332 **providers. Such monitoring should include daily observation by families and caregivers.**

333 Prescriptions for ZYBAN should be written for the smallest quantity of tablets consistent with
334 good patient management, in order to reduce the risk of overdose. Families and caregivers of
335 adults being treated for depression should be similarly advised.

336 **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial
337 presentation of bipolar disorder. It is generally believed (though not established in controlled
338 trials) that treating such an episode with an antidepressant alone may increase the likelihood of
339 precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the
340 symptoms described above represent such a conversion is unknown. However, prior to initiating
341 treatment with an antidepressant, patients with depressive symptoms should be adequately
342 screened to determine if they are at risk for bipolar disorder; such screening should include a
343 detailed psychiatric history, including a family history of suicide, bipolar disorder, and
344 depression. It should be noted that ZYBAN is not approved for use in treating bipolar
345 depression.

346 **Patients should be made aware that ZYBAN contains the same active ingredient**
347 **found in WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL used to treat**
348 **depression, and that ZYBAN should not be used in combination with WELLBUTRIN**
349 **(bupropion hydrochloride), the immediate release formulation; WELLBUTRIN SR**
350 **(bupropion hydrochloride), the sustained-release formulation; WELLBUTRIN XL**
351 **(bupropion hydrochloride), the extended-release formulation; or any other medications**
352 **that contain bupropion.**

353

354 **Seizures:** Because the use of bupropion is associated with a dose-dependent risk of
355 seizures, *clinicians should not prescribe doses over 300 mg/day for smoking cessation.* The
356 risk of seizures is also related to patient factors, clinical situation, and concomitant
357 medications, which must be considered in selection of patients for therapy with ZYBAN.
358 ZYBAN should be discontinued and not restarted in patients who experience a seizure
359 while on treatment.

360 • **Dose:** *For smoking cessation, doses above 300 mg/day should not be used.* The seizure
361 rate associated with doses of sustained-release bupropion up to 300 mg/day is
362 approximately 0.1% (1/1,000). This incidence was prospectively determined during an
363 8-week treatment exposure in approximately 3,100 depressed patients.

364 **Data for the immediate-release formulation of bupropion revealed a seizure**
365 **incidence of approximately 0.4% (4/1,000) in depressed patients treated at doses in a**
366 **range of 300 to 450 mg/day. In addition, the estimated seizure incidence increases**
367 **almost tenfold between 450 and 600 mg/day.**

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- 368 • **Patient factors:** Predisposing factors that may increase the risk of seizure with
369 bupropion use include history of head trauma or prior seizure, central nervous system
370 (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications
371 that lower seizure threshold.
- 372 • **Clinical situations:** Circumstances associated with an increased seizure risk include,
373 among others, excessive use of alcohol or sedatives (including benzodiazepines);
374 addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and
375 anorectics; and diabetes treated with oral hypoglycemics or insulin.
- 376 • **Concomitant medications:** Many medications (e.g., antipsychotics, antidepressants,
377 theophylline, systemic steroids) are known to lower seizure threshold.

378 **Recommendations for Reducing the Risk of Seizure:** Retrospective analysis of
379 clinical experience gained during the development of bupropion suggests that the risk of
380 seizure may be minimized if

- 381 • the total daily dose of ZYBAN does *not* exceed 300 mg (the maximum recommended
382 dose for smoking cessation), and
- 383 • the recommended daily dose for most patients (300 mg/day) is administered in divided
384 doses (150 mg twice daily).
- 385 • No single dose should exceed 150 mg to avoid high peak concentrations of bupropion
386 and/or its metabolites.

387 ZYBAN should be administered with extreme caution to patients with a history of
388 seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with
389 other agents (e.g., antipsychotics, antidepressants, theophylline, systemic steroids, etc.) that
390 lower seizure threshold.

391 **Hepatic Impairment:** ZYBAN should be used with extreme caution in patients with severe
392 hepatic cirrhosis. In these patients a reduced frequency of dosing is required, as peak
393 bupropion levels are substantially increased and accumulation is likely to occur in such
394 patients to a greater extent than usual. The dose should not exceed 150 mg every other day
395 in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE
396 AND ADMINISTRATION).

397 **Potential for Hepatotoxicity:** In rats receiving large doses of bupropion chronically, there
398 was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In
399 dogs receiving large doses of bupropion chronically, various histologic changes were seen in the
400 liver, and laboratory tests suggesting mild hepatocellular injury were noted.

401 PRECAUTIONS

402 **General: Allergic Reactions:** Anaphylactoid/anaphylactic reactions characterized by
403 symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have
404 been reported at a rate of about 1 to 3 per thousand in clinical trials of ZYBAN. In addition, there
405 have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson
406 syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking
407 ZYBAN and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions
408 (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

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409 Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed
410 hypersensitivity have been reported in association with bupropion. These symptoms may
411 resemble serum sickness.

412 **Insomnia:** In the dose-response smoking cessation trial, 29% of patients treated with
413 150 mg/day of ZYBAN and 35% of patients treated with 300 mg/day of ZYBAN experienced
414 insomnia, compared to 21% of placebo-treated patients. Symptoms were sufficiently severe to
415 require discontinuation of treatment in 0.6% of patients treated with ZYBAN and none of the
416 patients treated with placebo.

417 In the comparative trial, 40% of the patients treated with 300 mg/day of ZYBAN, 28% of
418 the patients treated with 21 mg/day of NTS, and 45% of the patients treated with the combination
419 of ZYBAN and NTS experienced insomnia compared to 18% of placebo-treated patients.
420 Symptoms were sufficiently severe to require discontinuation of treatment in 0.8% of patients
421 treated with ZYBAN and none of the patients in the other 3 treatment groups.

422 Insomnia may be minimized by avoiding bedtime doses and, if necessary, reduction in
423 dose.

424 **Psychosis, Confusion, and Other Neuropsychiatric Phenomena:** In clinical
425 trials with ZYBAN conducted in nondepressed smokers, the incidence of neuropsychiatric side
426 effects was generally comparable to placebo. Depressed patients treated with bupropion in
427 depression trials have been reported to show a variety of neuropsychiatric signs and symptoms
428 including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and
429 confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of
430 treatment.

431 **Activation of Psychosis and/or Mania:** Antidepressants can precipitate manic
432 episodes in bipolar disorder patients during the depressed phase of their illness and may activate
433 latent psychosis in other susceptible individuals. The sustained-release formulation of bupropion
434 is expected to pose similar risks. There were no reports of activation of psychosis or mania in
435 clinical trials with ZYBAN conducted in nondepressed smokers.

436 **Depression and Nicotine Withdrawal:** Depressed mood may be a symptom of
437 nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in patients
438 undergoing a smoking cessation attempt (**see WARNINGS: Clinical Worsening and Suicide
439 Risk**).

440 **Cardiovascular Effects:** In clinical practice, hypertension, in some cases severe,
441 requiring acute treatment, has been reported in patients receiving bupropion alone and in
442 combination with nicotine replacement therapy. These events have been observed in both
443 patients with and without evidence of preexisting hypertension.

444 Data from a comparative study of ZYBAN, nicotine transdermal system (NTS), the
445 combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking
446 cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with
447 the combination of ZYBAN and NTS. In this study, 6.1% of patients treated with the
448 combination of ZYBAN and NTS had treatment-emergent hypertension compared to 2.5%,
449 1.6%, and 3.1% of patients treated with ZYBAN, NTS, and placebo, respectively. The majority
450 of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the
451 combination of ZYBAN and NTS and 1 patient (0.4%) treated with NTS had study medication
452 discontinued due to hypertension compared to none of the patients treated with ZYBAN or
453 placebo. Monitoring of blood pressure is recommended in patients who receive the combination
454 of bupropion and nicotine replacement.

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455 There is no clinical experience establishing the safety of ZYBAN in patients with a recent
456 history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if
457 it is used in these groups. Bupropion was well tolerated in depressed patients who had previously
458 developed orthostatic hypotension while receiving tricyclic antidepressants, and was also
459 generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure
460 (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of
461 patients with CHF, resulting in discontinuation of treatment in 2 patients for exacerbation of
462 baseline hypertension.

463 **Hepatic Impairment:** ZYBAN should be used with extreme caution in patients with
464 severe hepatic cirrhosis. In these patients, a reduced frequency of dosing is required. ZYBAN
465 should be used with caution in patients with hepatic impairment (including mild to moderate
466 hepatic cirrhosis) and reduced frequency of dosing should be considered in patients with mild to
467 moderate hepatic cirrhosis.

468 All patients with hepatic impairment should be closely monitored for possible adverse
469 effects that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY,
470 WARNINGS, and DOSAGE AND ADMINISTRATION).

471 **Renal Impairment:** There is limited information on the pharmacokinetics of bupropion
472 in patients with renal impairment. An inter-study comparison between normal subjects and
473 patients with end-stage renal failure demonstrated that the parent drug C_{max} and AUC values
474 were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion
475 metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage
476 renal failure. Bupropion is extensively metabolized in the liver to active metabolites, which are
477 further metabolized and subsequently excreted by the kidneys. ZYBAN should be used with
478 caution in patients with renal impairment and a reduced frequency of dosing should be
479 considered as bupropion and the metabolites of bupropion may accumulate in such patients to a
480 greater extent than usual. The patient should be closely monitored for possible adverse effects
481 that could indicate high drug or metabolite levels.

482 **Information for Patients:** Although ZYBAN is not indicated for treatment of depression, it
483 contains the same active ingredient as the antidepressant medications WELLBUTRIN,
484 WELLBUTRIN SR, and WELLBUTRIN XL. Prescribers or other health professionals should
485 inform patients, their families, and their caregivers about the benefits and risks associated with
486 treatment with ZYBAN and should counsel them in its appropriate use. A Medication Guide
487 about using antidepressants in children and teenagers and important information about using
488 ZYBAN will be dispensed by the pharmacist with each new prescription and refill of ZYBAN.
489 The prescriber or health professional should instruct patients, their families, and their caregivers
490 to read the Medication Guide and should assist them in understanding its contents. Patients
491 should be given the opportunity to discuss the contents of the Medication Guide and to obtain
492 answers to any questions they may have. The complete text of the Medication Guide is reprinted
493 at the end of this document.

494 Patients should be advised of the following issues and asked to alert their prescriber if
495 these occur while taking ZYBAN.

496 **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers
497 should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia,
498 irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness),
499 hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal
500 ideation, especially early during antidepressant treatment and when the dose is adjusted up or

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501 down. Families and caregivers of patients should be advised to observe for the emergence of
502 such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be
503 reported to the patient's prescriber or health professional, especially if they are severe, abrupt in
504 onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be
505 associated with an increased risk for suicidal thinking and behavior and indicate a need for very
506 close monitoring and possibly changes in the medication.

507 Patients should be made aware that ZYBAN contains the same active ingredient found in
508 WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL used to treat depression and that
509 ZYBAN should not be used in conjunction with WELLBUTRIN, the immediate-release
510 formulation; WELLBUTRIN SR, the sustained-release formulation; WELLBUTRIN XL, the
511 extended-release formulation; or any other medications that contain bupropion hydrochloride.

512 **Laboratory Tests:** There are no specific laboratory tests recommended.

513 **Drug Interactions:** In vitro studies indicate that bupropion is primarily metabolized to
514 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug
515 interaction between ZYBAN and drugs that are substrates or inhibitors of the CYP2B6
516 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro studies
517 suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir,
518 ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been
519 performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not
520 appear to be produced by the cytochrome P450 isoenzymes. Few systemic data have been
521 collected on the metabolism of ZYBAN following concomitant administration with other drugs
522 or, alternatively, the effect of concomitant administration of ZYBAN on the metabolism of other
523 drugs.

524 Multiple oral doses of bupropion had no statistically significant effects on the single dose
525 pharmacokinetics of lamotrigine in 12 healthy volunteers.

526 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes
527 in humans. However, following chronic administration of bupropion, 100 mg t.i.d to 8 healthy
528 male volunteers for 14 days, there was no evidence of induction of its own metabolism. Because
529 bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical
530 activity. In particular, certain drugs may induce the metabolism of bupropion (e.g.,
531 carbamazepine, phenobarbital, phenytoin), while other drugs may inhibit the metabolism of
532 bupropion (e.g., cimetidine). The effects of concomitant administration of cimetidine on the
533 pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male
534 volunteers. Following oral administration of two 150-mg ZYBAN tablets with and without
535 800 mg of cimetidine, the pharmacokinetics of bupropion and its hydroxy metabolite were
536 unaffected. However, there were 16% and 32% increases, respectively, in the AUC and C_{max} of
537 the combined moieties of threohydro- and erythrohydro- bupropion.

538 **Drugs Metabolized by Cytochrome P450IID6 (CYP2D6):** Many drugs, including
539 most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics
540 are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this
541 isoenzyme, bupropion and hydroxybupropion are inhibitors of the CYP2D6 isoenzyme in vitro.
542 In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the
543 CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single
544 dose of 50 mg desipramine increased the C_{max} , AUC, and $t_{1/2}$ of desipramine by an average of
545 approximately 2-, 5- and 2-fold, respectively. The effect was present for at least 7 days after the

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546 last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6
547 has not been formally studied.

548 Therefore, co-administration of bupropion with drugs that are metabolized by CYP2D6
549 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine,
550 paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine),
551 beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide),
552 should be approached with caution and should be initiated at the lower end of the dose range of
553 the concomitant medication. If bupropion is added to the treatment regimen of a patient already
554 receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original
555 medication should be considered, particularly for those concomitant medications with a narrow
556 therapeutic index.

557 **MAO Inhibitors:** Studies in animals demonstrate that the acute toxicity of bupropion is
558 enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

559 **Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of
560 adverse experiences in patients receiving bupropion concurrently with either levodopa or
561 amantadine. Administration of ZYBAN to patients receiving either levodopa or amantadine
562 concurrently should be undertaken with caution, using small initial doses and gradual dose
563 increases.

564 **Drugs that Lower Seizure Threshold:** Concurrent administration of ZYBAN and
565 agents (e.g., antipsychotics, antidepressants, theophylline, systemic steroids, etc.) that lower
566 seizure threshold should be undertaken only with extreme caution (see WARNINGS).

567 **Nicotine Transdermal System:** (see PRECAUTIONS: Cardiovascular Effects).

568 **Smoking Cessation:** Physiological changes resulting from smoking cessation itself,
569 with or without treatment with ZYBAN, may alter the pharmacokinetics of some concomitant
570 medications, which may require dosage adjustment. Blood concentrations of concomitant
571 medications that are extensively metabolized, such as theophylline and warfarin, may be
572 expected to increase following smoking cessation due to de-induction of hepatic enzymes.

573 **Alcohol:** In post-marketing experience, there have been rare reports of adverse
574 neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol
575 during treatment with ZYBAN. The consumption of alcohol during treatment with ZYBAN
576 should be minimized or avoided (also see CONTRAINDICATIONS).

577 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies
578 were performed in rats and mice at doses up to 300 and 150 mg/kg per day, respectively. These
579 doses are approximately 10 and 2 times the maximum recommended human dose (MRHD),
580 respectively, on a mg/m² basis. In the rat study, there was an increase in nodular proliferative
581 lesions of the liver at doses of 100 to 300 mg/kg per day (approximately 3 to 10 times the
582 MRHD on a mg/m² basis); lower doses were not tested. The question of whether or not such
583 lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions
584 were not seen in the mouse study, and no increase in malignant tumors of the liver and other
585 organs was seen in either study.

586 Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5
587 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1
588 of 3 in vivo rat bone marrow cytogenetic studies.

589 A fertility study in rats at doses up to 300 mg/kg revealed no evidence of impaired
590 fertility.

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591 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. In studies conducted in rats and
592 rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively
593 (approximately 14 and 10 times the maximum recommended human dose [MRHD], respectively,
594 on a mg/m² basis), during the period of organogenesis. No clear evidence of teratogenic activity
595 was found in either species; however, in rabbits, slightly increased incidences of fetal
596 malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day,
597 approximately 2 times the MRHD on a mg/m² basis) and greater. Decreased fetal weights were
598 seen at 50 mg/kg and greater.

599 When rats were administered bupropion at oral doses of up to 300 mg/kg/day
600 (approximately 10 times the MRHD on a mg/m² basis) prior to mating and throughout pregnancy
601 and lactation, there were no apparent adverse effects on offspring development.

602 One study has been conducted in pregnant women. This retrospective, managed-care
603 database study assessed the risk of congenital malformations overall, and cardiovascular
604 malformations specifically, following exposure to bupropion in the first trimester compared to
605 the risk of these malformations following exposure to other antidepressants in the first trimester
606 and bupropion outside of the first trimester. This study included 7,005 infants with
607 antidepressant exposure during pregnancy, 1,213 of whom were exposed to bupropion in the first
608 trimester. The study showed no greater risk for congenital malformations overall, or
609 cardiovascular malformations specifically, following first trimester bupropion exposure
610 compared to exposure to all other antidepressants in the first trimester, or bupropion outside of
611 the first trimester. The results of this study have not been corroborated. ZYBAN should be used
612 during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnant
613 smokers should be encouraged to attempt cessation using educational and behavioral
614 interventions before pharmacological approaches are used.

615 To monitor fetal outcomes of pregnant women exposed to ZYBAN, GlaxoSmithKline
616 maintains a Bupropion Pregnancy Registry. Health care providers are encouraged to register
617 patients by calling (800) 336-2176.

618 **Labor and Delivery:** The effect of ZYBAN on labor and delivery in humans is unknown.

619 **Nursing Mothers:** Bupropion and its metabolites are secreted in human milk. Because of the
620 potential for serious adverse reactions in nursing infants from ZYBAN, a decision should be
621 made whether to discontinue nursing or to discontinue the drug, taking into account the
622 importance of the drug to the mother.

623 **Pediatric Use:** Safety and effectiveness in the pediatric population have not been established
624 (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Anyone
625 considering the use of ZYBAN in a child or adolescent must balance the potential risks with the
626 clinical need.

627 **Geriatric Use:** Of the approximately 6,000 patients who participated in clinical trials with
628 bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and
629 over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in
630 clinical trials using the immediate-release formulation of bupropion (depression studies). No
631 overall differences in safety or effectiveness were observed between these subjects and younger
632 subjects, and other reported clinical experience has not identified differences in responses
633 between the elderly and younger patients, but greater sensitivity of some older individuals cannot
634 be ruled out.

635 A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and
636 its metabolites in elderly subjects was similar to that of younger subjects; however, another

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637 pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased
638 risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).

639 Bupropion is extensively metabolized in the liver to active metabolites, which are further
640 metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in
641 patients with impaired renal function. Because elderly patients are more likely to have decreased
642 renal function, care should be taken in dose selection, and it may be useful to monitor renal
643 function (see PRECAUTIONS: Renal Impairment and DOSAGE AND ADMINISTRATION).

644 **ADVERSE REACTIONS** (see also WARNINGS and PRECAUTIONS)

645 The information included under ADVERSE REACTIONS is based primarily on data
646 from the dose-response trial and the comparative trial that evaluated ZYBAN for smoking
647 cessation (see CLINICAL TRIALS). Information on additional adverse events associated with
648 the sustained-release formulation of bupropion in depression trials, as well as the
649 immediate-release formulation of bupropion, is included in a separate section (see Other Events
650 Observed During the Clinical Development and Postmarketing Experience of Bupropion).

651 **Adverse Events Associated With the Discontinuation of Treatment:** Adverse events
652 were sufficiently troublesome to cause discontinuation of treatment in 8% of the 706 patients
653 treated with ZYBAN and 5% of the 313 patients treated with placebo. The more common events
654 leading to discontinuation of treatment with ZYBAN included nervous system disturbances
655 (3.4%), primarily tremors, and skin disorders (2.4%), primarily rashes.

656 **Incidence of Commonly Observed Adverse Events:** The most commonly observed
657 adverse events consistently associated with the use of ZYBAN were dry mouth and insomnia.
658 The most commonly observed adverse events were defined as those that consistently occurred at
659 a rate of 5 percentage points greater than that for placebo across clinical studies.

660 **Dose Dependency of Adverse Events:** The incidence of dry mouth and insomnia may be
661 related to the dose of ZYBAN. The occurrence of these adverse events may be minimized by
662 reducing the dose of ZYBAN. In addition, insomnia may be minimized by avoiding bedtime
663 doses.

664 **Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated
665 With ZYBAN:** Table 4 enumerates selected treatment-emergent adverse events from the
666 dose-response trial that occurred at an incidence of 1% or more and were more common in
667 patients treated with ZYBAN compared to those treated with placebo. Table 5 enumerates
668 selected treatment-emergent adverse events from the comparative trial that occurred at an
669 incidence of 1% or more and were more common in patients treated with ZYBAN, NTS, or the
670 combination of ZYBAN and NTS compared to those treated with placebo. Reported adverse
671 events were classified using a COSTART-based dictionary.

672

673 **Table 4. Treatment-Emergent Adverse Event Incidence in the Dose-Response Trial***

Body System/ Adverse Experience	ZYBAN 100 to 300 mg/day (n = 461) %	Placebo (n = 150) %
Body (General)		
Neck pain	2	<1
Allergic reaction	1	0
Cardiovascular	1	0

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Hot flashes	1	<1
Hypertension		
Digestive		
Dry mouth	11	5
Increased appetite	2	<1
Anorexia	1	<1
Musculoskeletal		
Arthralgia	4	3
Myalgia	2	1
Nervous system		
Insomnia	31	21
Dizziness	8	7
Tremor	2	1
Somnolence	2	1
Thinking abnormality	1	0
Respiratory		
Bronchitis	2	0
Skin		
Pruritus	3	<1
Rash	3	<1
Dry skin	2	0
Urticaria	1	0
Special senses		
Taste perversion	2	<1

674 * Selected adverse events with an incidence of at least 1% of patients treated with ZYBAN
675 and more frequent than in the placebo group.
676

677 **Table 5. Treatment-Emergent Adverse Event Incidence in the Comparative Trial***

Adverse Experience (COSTART Term)	ZYBAN 300 mg/day (n = 243) %	Nicotine Transdermal System (NTS) 21 mg/day (n = 243) %	ZYBAN and NTS (n = 244) %	Placebo (n = 159) %
Body				
Abdominal pain	3	4	1	1
Accidental injury	2	2	1	1
Chest pain	<1	1	3	1
Neck pain	2	1	<1	0
Facial edema	<1	0	1	0
Cardiovascular				
Hypertension	1	<1	2	0
Palpitations	2	0	1	0
Digestive				

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Nausea	9	7	11	4
Dry mouth	10	4	9	4
Constipation	8	4	9	3
Diarrhea	4	4	3	1
Anorexia	3	1	5	1
Mouth ulcer	2	1	1	1
Thirst	<1	<1	2	0
Musculoskeletal				
Myalgia	4	3	5	3
Arthralgia	5	3	3	2
Nervous system				
Insomnia	40	28	45	18
Dream abnormality	5	18	13	3
Anxiety	8	6	9	6
Disturbed concentration	9	3	9	4
Dizziness	10	2	8	6
Nervousness	4	<1	2	2
Tremor	1	<1	2	0
Dysphoria	<1	1	2	1
Respiratory				
Rhinitis	12	11	9	8
Increased cough	3	5	<1	1
Pharyngitis	3	2	3	0
Sinusitis	2	2	2	1
Dyspnea	1	0	2	1
Epistaxis	2	1	1	0
Skin				
Application site reaction [†]	11	17	15	7
Rash	4	3	3	2
Pruritus	3	1	5	1
Urticaria	2	0	2	0
Special Senses				
Taste perversion	3	1	3	2
Tinnitus	1	0	<1	0

678 * Selected adverse events with an incidence of at least 1% of patients treated with either ZYBAN,
679 NTS, or the combination of ZYBAN and NTS and more frequent than in the placebo group.

680 [†] Patients randomized to ZYBAN or placebo received placebo patches.

681

682 ZYBAN was well-tolerated in the long-term maintenance trial that evaluated chronic
683 administration of ZYBAN for up to 1 year and in the COPD trial that evaluated patients with
684 mild-to-moderate COPD for a 12-week period. Adverse events in both studies were
685 quantitatively and qualitatively similar to those observed in the dose-response and comparative
686 trials.

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687 **Other Events Observed During the Clinical Development and Postmarketing**
688 **Experience of Bupropion:**

689 In addition to the adverse events noted above, the following
690 events have been reported in clinical trials and postmarketing experience with the
691 sustained-release formulation of bupropion in depressed patients and in nondepressed smokers,
692 as well as in clinical trials and postmarketing clinical experience with the immediate-release
693 formulation of bupropion.

694 Adverse events for which frequencies are provided below occurred in clinical trials with
695 bupropion sustained-release. The frequencies represent the proportion of patients who
696 experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled
697 studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced
698 an adverse event requiring discontinuation of treatment in an open-label surveillance study with
699 bupropion sustained-release tablets (n = 3,100). All treatment-emergent adverse events are
700 included except those listed in Tables 4 and 5, those events listed in other safety-related sections
701 of the insert, those adverse events subsumed under COSTART terms that are either overly
702 general or excessively specified so as to be uninformative, those events not reasonably associated
703 with the use of the drug, and those events that were not serious and occurred in fewer than
704 2 patients.

705 Events are further categorized by body system and listed in order of decreasing frequency
706 according to the following definitions of frequency: Frequent adverse events are defined as those
707 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to
708 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

709 Adverse events for which frequencies are not provided occurred in clinical trials or
710 postmarketing experience with bupropion. Only those adverse events not previously listed for
711 sustained-release bupropion are included. The extent to which these events may be associated
712 with ZYBAN is unknown.

713 **Body (General):** Frequent were asthenia, fever, and headache. Infrequent were back
714 pain, chills, inguinal hernia, musculoskeletal chest pain, pain, and photosensitivity. Rare was
715 malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms
716 suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see
717 PRECAUTIONS).

718 **Cardiovascular:** Infrequent were flushing, migraine, postural hypotension, stroke,
719 tachycardia, and vasodilation. Rare was syncope. Also observed were cardiovascular disorder,
720 complete AV block, extrasystoles, hypotension, hypertension (in some cases severe, see
721 PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

722 **Digestive:** Frequent were dyspepsia, flatulence, and vomiting. Infrequent were
723 abnormal liver function, bruxism, dysphagia, gastric reflux, gingivitis, glossitis, jaundice, and
724 stomatitis. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal
725 hemorrhage, gum hemorrhage, hepatitis, increased salivation, intestinal perforation, liver
726 damage, pancreatitis, stomach ulcer, and stool abnormality.

727 **Endocrine:** Also observed were hyperglycemia, hypoglycemia, and syndrome of
728 inappropriate antidiuretic hormone.

729 **Hemic and Lymphatic:** Infrequent was ecchymosis. Also observed were anemia,
730 leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT
731 and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were
732 observed when bupropion was co-administered with warfarin.

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732 **Metabolic and Nutritional:** Infrequent were edema, increased weight, and peripheral
733 edema. Also observed was glycosuria.

734 **Musculoskeletal:** Infrequent were leg cramps and twitching. Also observed were
735 arthritis and muscle rigidity/fever/rhabdomyolysis, and muscle weakness.

736 **Nervous System:** Frequent were agitation, depression, and irritability. Infrequent were
737 abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory,
738 depersonalization, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia,
739 paresthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and
740 hypomania. Also observed were abnormal electroencephalogram (EEG), aggression, akinesia,
741 aphasia, coma, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal
742 syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy,
743 paranoid ideation, restlessness, and unmasking tardive dyskinesia.

744 **Respiratory:** Rare was bronchospasm. Also observed was pneumonia.

745 **Skin:** Frequent was sweating. Infrequent was acne and dry skin. Rare was maculopapular
746 rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.

747 **Special Senses:** Frequent was blurred vision or diplopia. Infrequent were
748 accommodation abnormality and dry eye. Also observed were deafness, increased intraocular
749 pressure, and mydriasis.

750 **Urogenital:** Frequent was urinary frequency. Infrequent were impotence, polyuria, and
751 urinary urgency. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria,
752 gynecomastia, menopause, painful erection, prostate disorder, salpingitis, urinary incontinence,
753 urinary retention, urinary tract disorder, and vaginitis.

754 DRUG ABUSE AND DEPENDENCE

755 ZYBAN is likely to have a low abuse potential.

756 **Humans:** There have been few reported cases of drug dependence and withdrawal symptoms
757 associated with the immediate-release formulation of bupropion. In human studies of abuse
758 liability, individuals experienced with drugs of abuse reported that bupropion produced a feeling
759 of euphoria and desirability. In these subjects, a single dose of 400 mg (1.33 times the
760 recommended daily dose) of bupropion produced mild amphetamine-like effects compared to
761 placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories
762 (ARCI), which is indicative of euphorogenic properties and a score intermediate between placebo
763 and amphetamine on the Liking Scale of the ARCI.

764 **Animals:** Studies in rodents and primates have shown that bupropion exhibits some
765 pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase
766 locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of
767 responding in several schedule-controlled behavior paradigms. In primate models to assess the
768 positive reinforcing effects of psychoactive drugs, bupropion was self-administered
769 intravenously. In rats, bupropion produced amphetamine- and cocaine-like discriminative
770 stimulus effects in drug discrimination paradigms used to characterize the subjective effects of
771 psychoactive drugs.

772 The possibility that bupropion may induce dependence should be kept in mind when
773 evaluating the desirability of including the drug in smoking cessation programs of individual
774 patients.

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775 **OVERDOSAGE**

776 **Human Overdose Experience:** Overdoses of up to 30 g or more of bupropion have been
777 reported. Seizure was reported in approximately one third of all cases. Other serious reactions
778 reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus
779 tachycardia, and ECG changes such as conduction disturbances or arrhythmias. Fever, muscle
780 rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported
781 mainly when bupropion was part of multiple drug overdoses.

782 Although most patients recovered without sequelae, deaths associated with overdoses of
783 bupropion alone have been reported in patients ingesting large doses of the drug. Multiple
784 uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported
785 in these patients.

786 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.
787 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first
788 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.
789 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with
790 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in
791 symptomatic patients.

792 Activated charcoal should be administered. There is no experience with the use of forced
793 diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion
794 overdoses. No specific antidotes for bupropion are known.

795 Due to the dose-related risk of seizures with ZYBAN, hospitalization following suspected
796 overdose should be considered. Based on studies in animals, it is recommended that seizures be
797 treated with intravenous benzodiazepine administration and other supportive measures, as
798 appropriate.

799 In managing overdosage, consider the possibility of multiple drug involvement. The
800 physician should consider contacting a poison control center for additional information on the
801 treatment of any overdose. Telephone numbers for certified poison control centers are listed in
802 the *Physicians' Desk Reference* (PDR).

803 **DOSAGE AND ADMINISTRATION**

804 **Usual Dosage for Adults:** The recommended and maximum dose of ZYBAN is 300 mg/day,
805 given as 150 mg twice daily. Dosing should begin at 150 mg/day given every day for the first
806 3 days, followed by a dose increase for most patients to the recommended usual dose of
807 300 mg/day. There should be an interval of at least 8 hours between successive doses. Doses
808 above 300 mg/day should not be used (see WARNINGS). ZYBAN should be swallowed whole
809 and not crushed, divided, or chewed. Treatment with ZYBAN should be initiated **while the**
810 **patient is still smoking**, since approximately 1 week of treatment is required to achieve
811 steady-state blood levels of bupropion. Patients should set a "target quit date" within the first
812 2 weeks of treatment with ZYBAN, generally in the second week. Treatment with ZYBAN
813 should be continued for 7 to 12 weeks; longer treatment should be guided by the relative benefits
814 and risks for individual patients. If a patient has not made significant progress towards
815 abstinence by the seventh week of therapy with ZYBAN, it is unlikely that he or she will quit
816 during that attempt, and treatment should probably be discontinued. Conversely, a patient who
817 successfully quits after 7 to 12 weeks of treatment should be considered for ongoing therapy with
818 ZYBAN. Dose tapering of ZYBAN is not required when discontinuing treatment. It is important

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819 that patients continue to receive counseling and support throughout treatment with ZYBAN, and
820 for a period of time thereafter.

821 **Individualization of Therapy:** Patients are more likely to quit smoking and remain abstinent
822 if they are seen frequently and receive support from their physicians or other health care
823 professionals. It is important to ensure that patients read the instructions provided to them and
824 have their questions answered. Physicians should review the patient's overall smoking cessation
825 program that includes treatment with ZYBAN. Patients should be advised of the importance of
826 participating in the behavioral interventions, counseling, and/or support services to be used in
827 conjunction with ZYBAN. See information for patients at the end of the package insert.

828 The goal of therapy with ZYBAN is complete abstinence. If a patient has not made
829 significant progress towards abstinence by the seventh week of therapy with ZYBAN, it is
830 unlikely that he or she will quit during that attempt, and treatment should probably be
831 discontinued.

832 Patients who fail to quit smoking during an attempt may benefit from interventions to
833 improve their chances for success on subsequent attempts. Patients who are unsuccessful should
834 be evaluated to determine why they failed. A new quit attempt should be encouraged when
835 factors that contributed to failure can be eliminated or reduced, and conditions are more
836 favorable.

837 **Maintenance:** Nicotine dependence is a chronic condition. Some patients may need
838 continuous treatment. Systematic evaluation of ZYBAN 300 mg/day for maintenance therapy
839 demonstrated that treatment for up to 6 months was efficacious. Whether to continue treatment
840 with ZYBAN for periods longer than 12 weeks for smoking cessation must be determined for
841 individual patients.

842 **Combination Treatment With ZYBAN and a Nicotine Transdermal System (NTS):**
843 Combination treatment with ZYBAN and NTS may be prescribed for smoking cessation. The
844 prescriber should review the complete prescribing information for both ZYBAN and NTS before
845 using combination treatment. See also CLINICAL TRIALS for methods and dosing used in the
846 ZYBAN and NTS combination trial. Monitoring for treatment-emergent hypertension in patients
847 treated with the combination of ZYBAN and NTS is recommended.

848 **Dosage Adjustment for Patients with Impaired Hepatic Function:** ZYBAN should be
849 used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed
850 150 mg every other day in these patients. ZYBAN should be used with caution in patients with
851 hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency of
852 dosing should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL
853 PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

854 **Dosage Adjustment for Patients with Impaired Renal Function:** ZYBAN should be
855 used with caution in patients with renal impairment and a reduced frequency of dosing should be
856 considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

857 HOW SUPPLIED

858 ZYBAN Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are purple,
859 round, biconvex, film-coated tablets printed with "ZYBAN 150" in bottles of 60 (NDC 0173-
860 0556-02) tablets and the ZYBAN Advantage Pack[®] containing 1 bottle of 60 (NDC 0173-0556-
861 01) tablets.

862 **Store at controlled room temperature, 20° to 25°C (68° to 77°F) (see USP). Dispense**
863 **in tight, light-resistant containers as defined in the USP.**

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864

865

MEDICATION GUIDE

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ZYBAN[®] (zi ban)

867

(bupropion hydrochloride) Sustained-Release Tablets

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Read this Medication Guide carefully before you start using ZYBAN and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about ZYBAN, ask your doctor or pharmacist.

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IMPORTANT: Be sure to read the section of this Medication Guide beginning with “What is the most important information I should know about ZYBAN?” It contains important information about this medication. It immediately follows the next section called “About Using Antidepressants in Children and Teenagers.”

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About Using Antidepressants in Children and Teenagers

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881

What is the most important information I should know if my child is being prescribed an antidepressant?

882

883

884

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

885

886

1. There is a risk of suicidal thoughts or actions

887

2. How to try to prevent suicidal thoughts or actions in your child

888

3. You should watch for certain signs if your child is taking an antidepressant

889

4. There are benefits and risks when using antidepressants

890

891

1. There is a Risk of Suicidal Thoughts or Actions

892

893

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

894

895

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

896

897

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899

900

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

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For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

907

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- 908 • Bipolar illness (sometimes called manic-depressive illness)
909 • A family history of bipolar illness
910 • A personal or family history of attempting suicide
911 If any of these are present, make sure you tell your healthcare provider before your child takes an
912 antidepressant.
913

914 **2. How to Try to Prevent Suicidal Thoughts and Actions**

915

916 To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her
917 or his moods or actions, especially if the changes occur suddenly. Other important people in your
918 child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers,
919 and other important people). The changes to look out for are listed in Section 3, on what to watch
920 for.

921 Whenever an antidepressant is started or its dose is changed, pay close attention to your child.
922 After starting an antidepressant, your child should generally see his or her healthcare provider:

- 924 • Once a week for the first 4 weeks
925 • Every 2 weeks for the next 4 weeks
926 • After taking the antidepressant for 12 weeks
927 • After 12 weeks, follow your healthcare provider's advice about how often to come back
928 • More often if problems or questions arise (see Section 3)
929

930 You should call your child's healthcare provider between visits if needed.
931

932 **3. You Should Watch For Certain Signs if Your Child is Taking an Antidepressant**

933

934 Contact your child's healthcare provider *right away* if your child exhibits any of the following
935 signs for the first time, or they seem worse, or worry you, your child, or your child's teacher:

- 936 • Thoughts about suicide or dying
937 • Attempts to commit suicide
938 • New or worse depression
939 • New or worse anxiety
940 • Feeling very agitated or restless
941 • Panic attacks
942 • Difficulty sleeping (insomnia)
943 • New or worse irritability
944 • Acting aggressive, being angry, or violent
945 • Acting on dangerous impulses
946 • An extreme increase in activity and talking
947 • Other unusual changes in behavior or mood
948

949 Never let your child stop taking an antidepressant without first talking to his or her healthcare
950 provider. Stopping an antidepressant suddenly can cause other symptoms.

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951

952 **4. There are Benefits and Risks When Using Antidepressants**

953

954 Antidepressants are used to treat depression and other illnesses. Depression and other illnesses
955 can lead to suicide. In some children and teenagers, treatment with an antidepressant increases
956 suicidal thinking or actions. It is important to discuss all the risks of treating depression and also
957 the risks of not treating it. You and your child should discuss all treatment choices with your
958 healthcare provider, not just the use of antidepressants.

959

960 Other side effects can occur with antidepressants (see section below).

961

962 Of all antidepressants, only fluoxetine (PROZAC®)* has been FDA approved to treat pediatric
963 depression.

964

965 For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine
966 (PROZAC®)*, sertraline (ZOLOFT®)*, fluvoxamine (LUVOX®)*, and clomipramine
967 (ANAFRANIL®)*.

968

969 Your healthcare provider may suggest other antidepressants based on the past experience of your
970 child or other family members.

971

972 **Is this all I need to know if my child is being prescribed an antidepressant?**

973

974 No. This is a warning about the risk of suicidality. Other side effects can occur with
975 antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the
976 particular drug he or she is prescribing. Also ask about drugs to avoid when taking an
977 antidepressant. Ask your healthcare provider or pharmacist where to find more information.

978

979 **What is the most important information I should know about ZYBAN?**

980

981 **There is a chance of having a seizure (convulsion, fit) with ZYBAN, especially in people:**

982

- with certain medical problems.
- who take certain medicines.

984

985 The chance of having seizures increases with higher doses of ZYBAN. For more information,
986 see the sections “Who should not take ZYBAN?” and “What should I tell my doctor before using
987 ZYBAN?” Tell your doctor about all of your medical conditions and all the medicines you take.

988 **Do not take any other medicines while you are using ZYBAN unless your doctor has said it
989 is okay to take them.**

990

991 **If you have a seizure while taking ZYBAN, stop taking the tablets and call your doctor
992 right away.** Do not take ZYBAN again if you have a seizure.

993

994 **What is important information I should know and share with my family about taking
995 antidepressants?**

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996 Although ZYBAN is not a treatment for depression, it contains the same active ingredient as the
997 antidepressant medications WELLBUTRIN[®], WELLBUTRIN SR[®], and WELLBUTRIN XL[®].
998 Therefore, you should be aware of the following information. Patients taking antidepressants,
999 and their families, should watch out for worsening depression or thoughts of suicide. Also watch
1000 out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable,
1001 hostile, aggressive, impulsive, severely restless, overly excited and hyperactive, not being able to
1002 sleep, or other unusual changes in behavior. If this happens, especially at the beginning of
1003 antidepressant treatment or after a change in dose, call your doctor. For additional information,
1004 see section above entitled "About Using Antidepressants in Children and Teenagers." ZYBAN
1005 has not been studied in children under the age of 18 and is not approved for use in children and
1006 teenagers.

1007

1008 **What is ZYBAN?**

1009 ZYBAN is a prescription medicine to help people quit smoking. Studies have shown that more
1010 than one third of people quit smoking for at least 1 month while taking ZYBAN and participating
1011 in a patient support program. For many patients, ZYBAN reduces withdrawal symptoms and the
1012 urge to smoke. ZYBAN should be used with a patient support program. It is important to
1013 participate in the behavioral program, counseling, or other support program your health care
1014 professional recommends.

1015

1016 **Who should not take ZYBAN?**

1017 **Do not take ZYBAN if you:**

- 1018 • have or had a seizure disorder or epilepsy.
- 1019 • **are taking WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, or any other**
1020 **medicines that contain bupropion hydrochloride.** Bupropion is the same active ingredient
1021 that is in ZYBAN.
- 1022 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these
1023 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 1024 • have taken within the last 14 days medicine for depression called a monoamine oxidase
1025 inhibitor (MAOI), such as NARDIL^{®*} (phenelzine sulfate), PARNATE[®] (tranylcypromine
1026 sulfate), or MARPLAN^{®*} (isocarboxazid).
- 1027 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1028 • are allergic to the active ingredient in ZYBAN, bupropion, or to any of the inactive
1029 ingredients. See the end of this leaflet for a complete list of ingredients in ZYBAN.

1030

1031 **Can I take ZYBAN if I have mild-to-moderate chronic bronchitis and/or emphysema (also** 1032 **called chronic obstructive pulmonary disease or COPD)?**

1033 Yes, ZYBAN combined with a behavior modification program has been shown to help people
1034 with COPD quit smoking. It is important to participate in the behavior program, counseling, or
1035 other support program your health care professional recommends.

1036

1037 **What should I tell my doctor before using ZYBAN?**

- 1038 • **Tell your doctor about your medical conditions.** Tell your doctor if you:

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- 1039 • **are pregnant or plan to become pregnant.** It is not known if ZYBAN can harm your
1040 unborn baby. If you can use ZYBAN while you are pregnant, talk to your doctor about
1041 how you can be on the Bupropion Pregnancy Registry.
- 1042 • **are breastfeeding.** ZYBAN passes through your milk. It is not known if ZYBAN can
1043 harm your baby.
- 1044 • **have liver problems,** especially cirrhosis of the liver.
- 1045 • have kidney problems.
- 1046 • have an eating disorder such as anorexia nervosa or bulimia.
- 1047 • have had a head injury.
- 1048 • have had a seizure (convulsion, fit).
- 1049 • have a tumor in your nervous system (brain or spine).
- 1050 • have had a heart attack, heart problems, or high blood pressure.
- 1051 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1052 • drink a lot of alcohol.
- 1053 • abuse prescription medicines or street drugs.
- 1054

- 1055 • **Tell your doctor about all the medicines you take,** including prescription and non-
1056 prescription medicines, vitamins, and herbal supplements. Many medicines increase your
1057 chances of getting seizures or other serious side effects if you take them while you are using
1058 ZYBAN.

1059

1060 **How should I take ZYBAN?**

- 1061 • Take ZYBAN exactly as prescribed by your doctor.
- 1062 • **Do not chew, cut, or crush ZYBAN Tablets.** You must swallow the tablets whole. **Tell**
1063 **your doctor if you cannot swallow medicine tablets.**
- 1064 • Take ZYBAN at the same time each day.
- 1065 • Take your doses of ZYBAN at least 8 hours apart.
- 1066 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and
1067 take your next tablet at the regular time. **This is very important.** Too much ZYBAN can
1068 increase your chance of having a seizure.
- 1069 • If you take too much ZYBAN, or overdose, call your local emergency room or poison
1070 control center right away.
- 1071 • **Do not take any other medicines while using ZYBAN unless your doctor has told you it**
1072 **is okay.**
- 1073 • Do not change your dose or stop taking ZYBAN without talking with your doctor first.
- 1074

1074

1075 **How long should I take ZYBAN?**

1076 Most people should take ZYBAN for at least 7 to 12 weeks. Some people may need to take
1077 ZYBAN for a longer period of time to assist in their smoking cessation efforts. Follow your
1078 doctor's instructions.

1079

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1080 **When should I stop smoking?**

1081 It takes about 1 week for ZYBAN to reach the right levels in your body to be effective. So, to
1082 maximize your chance of quitting, you should not stop smoking until you have been taking
1083 ZYBAN for 1 week. You should set a date to stop smoking during the second week you're
1084 taking ZYBAN.

1085

1086 **Can I smoke while taking ZYBAN?**

1087 It is not physically dangerous to smoke and use ZYBAN at the same time. However, continuing
1088 to smoke after the date you set to stop smoking will seriously reduce your chance of breaking
1089 your smoking habit.

1090

1091 **Can ZYBAN be used at the same time as nicotine patches?**

1092 Yes, ZYBAN and nicotine patches can be used at the same time but should only be used together
1093 under the supervision of your doctor. Using ZYBAN and nicotine patches together may raise
1094 your blood pressure, sometimes severely. Tell your doctor if you are planning to use nicotine
1095 replacement therapy because your doctor will probably want to check your blood pressure
1096 regularly to make sure that it stays within acceptable levels.

1097

1098 **DO NOT SMOKE AT ANY TIME** if you are using a nicotine patch or any other nicotine
1099 product along with ZYBAN. It is possible to get too much nicotine and have serious side effects.

1100

1101 **What should I avoid while taking ZYBAN?**

- 1102 • Do not drink a lot of alcohol while taking ZYBAN. If you usually drink a lot of alcohol, talk
1103 with your doctor before suddenly stopping. If you suddenly stop drinking alcohol, you may
1104 increase your chance of having seizures.
- 1105 • Do not drive a car or use heavy machinery until you know how ZYBAN affects you.
1106 ZYBAN can impair your ability to perform these tasks.

1107

1108 **What are possible side effects of ZYBAN?**

- 1109 • **Seizures.** Some patients get seizures while taking ZYBAN. **If you have a seizure while**
1110 **taking ZYBAN, stop taking the tablets and call your doctor right away.** Do not take
1111 ZYBAN again if you have a seizure.
- 1112 • **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes
1113 severe, while taking ZYBAN. The chance of high blood pressure may be increased if you
1114 also use nicotine replacement therapy (for example, a nicotine patch) to help you stop
1115 smoking (see "Can ZYBAN be used at the same time as nicotine patches?").
- 1116 • **Severe allergic reactions: Stop taking ZYBAN and call your doctor right away** if you get
1117 a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the
1118 eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be
1119 signs of a serious allergic reaction.
- 1120 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while
1121 taking ZYBAN, including delusions (believe you are someone else), hallucinations (seeing or

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1122 hearing things that are not there), paranoia (feeling that people are against you), or feeling
1123 confused. If this happens to you, call your doctor.

1124

1125 The most common side effects of ZYBAN are dry mouth and difficulty sleeping. These side
1126 effects are generally mild and often disappear after a few weeks. If you have difficulty sleeping,
1127 do not take your medicine too close to bedtime.

1128

1129 Tell your doctor right away about any side effects that bother you.

1130

1131 These are not all the side effects of ZYBAN. For a complete list, ask your doctor or pharmacist.

1132

1133 **How should I store ZYBAN?**

1134 • Store ZYBAN at room temperature. Store out of direct sunlight. Keep ZYBAN in its tightly
1135 closed bottle.

1136 • ZYBAN may have an odor.

1137

1138 **General Information about ZYBAN.**

1139 • Medicines are sometimes prescribed for purposes other than those listed in a Medication
1140 Guide. Do not use ZYBAN for a condition for which it was not prescribed. Do not give
1141 ZYBAN to other people, even if they have the same symptoms you have. It may harm them.
1142 Keep ZYBAN out of the reach of children.

1143

1144 This Medication Guide summarizes important information about ZYBAN. For more information,
1145 talk with your doctor. You can ask your doctor or pharmacist for information about ZYBAN that
1146 is written for health professionals.

1147

1148 **What are the ingredients in ZYBAN?**

1149 Active ingredient: bupropion hydrochloride.

1150

1151 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate,
1152 microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide. The tablets
1153 are printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake
1154 and FD&C Red No. 40 Lake.

1155

1156 *The following are registered trademarks of their respective manufacturers: PROZAC[®]/Eli Lilly
1157 and Company; ZOLOFT[®]/Pfizer Pharmaceuticals; LUVOX[®]/Solvay Pharmaceuticals, Inc;
1158 ANAFRANIL[®]/Mallinckrodt Inc; NARDIL[®]/Warner Lambert Company; MARPLAN[®]/Oxford
1159 Pharmaceutical Services, Inc.

1160

1161 **R_x only**

1162

1163 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1164

1165 September 2006

MG-ZY:2

1166

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